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Editorial

Immotile cilia

Large areas within our airways are covered with ciliated epithelia. A conservative estimate gives a figure of 0·5 m^2 with a total of 3×10^{12} cilia. Nobody who has seen these cilia alive can fail to be impressed by their rapid and incessant movements (about 20 cycles per second). Surely, ciliary work must be very important. The question is, how important? Most textbook authors seem to be of the opinion expressed by Hilding[1] in one of his classical studies. "Death may occur from failure of the ciliary system within the respiratory tract. In certain diseases of the lower respiratory tract, the cilia become destroyed and the ciliary function lost. Secretions collect, as a result, in such large quantities that the patients die of asphyxia."

We discuss here recent advances in the understanding of cilia that cast some doubt on the validity of this belief.

According to the classical concept of Lucas and Douglas,[2] which is still valid in its essentials, the secretions in the respiratory tract form two layers outside the ciliated cells. The inner stratum is a serous fluid in which the cilia beat while the outer one is the gel or mucous layer which is dragged along by the work of the cilia by direct contact during their active stroke. Each stratum is about 5 μm thick, which is also the length of the cilia in the respiratory tract.[3] Inhaled particles and endogenous debris are trapped in the mucous layer which is transported towards the pharynx and then normally swallowed. During acute irritation and in hypersecretory states, coughing is a very important clearance mechanism but this will not be discussed here.

During recent years methods have been developed to measure the efficiency of human mucociliary clearance. It has been shown that tracheobronchial or tracheal mucociliary clearance is usually severely impaired in patients with chronic bronchitis.[4–7] This impairment is often present already in cases of simple chronic bronchitis (without significant airways obstruction), and may be present in more or less symptom-free smokers.[7 8] Tracheal mucociliary transport has been found to be moderately decreased in symptom-free asthmatics and to be further decreased after antigen provocation.[9] However, in most asthmatics in stable phase the tracheobronchial mucociliary clearance has been found to be much better preserved than in patients with obstructive lung disease associated with chronic bronchitis.[10] The same has been found in patients with emphysema associated with alpha$_1$-antitrypsin deficiency if chronic bronchitis is not present.[11] Patients suffering from cystic fibrosis also usually have a depression of mucociliary clearance.[12]

The reasons for decreased mucociliary clearance in obstructive lung disease, chronic bronchitis in particular, has not been completely clarified. Although patchy loss of cilia, with or without squamous cell metaplasia, is probably common in chronic bronchitis,[13] it is not known whether such ciliary loss may be extensive enough to affect the overall mucociliary clearance. Structurally abnormal cilia may occur,[14–16] but it is doubtful whether such cilia may be common enough to affect mucociliary transport. On the other hand, it has become evident that the quantity and physical properties of respiratory tract secretions may be very important for the efficacy of mucociliary transport. The role of mucus elasticity for clearance has recently been dealt with in this journal.[17]

The opportunity to evaluate the role of mucociliary transport has recently emerged with the discovery and characterisation of a disease caused by congenital immotility of the cilia.[18–23] Before explaining the implications of this finding the fine structure of cilia should be described. The ciliary motor is called the axoneme (figure). It consists of nine microtubular doublets in a circle around two central microtubules. Each of the nine doublets has two rows of short projections, the dynein arms, and a long radial projection, the spoke. The doublets are joined by bonds, called the nexin links. The two central microtubules are partly surrounded by rib-like components, called the central sheath. The thickened end of the spoke (the spoke head) seems to articulate against the central sheath.

Address for reprint requests: Dr BA Afzelius, Wenner-Gren Institute, University of Stockholm, S–113 45 Stockholm, Sweden.

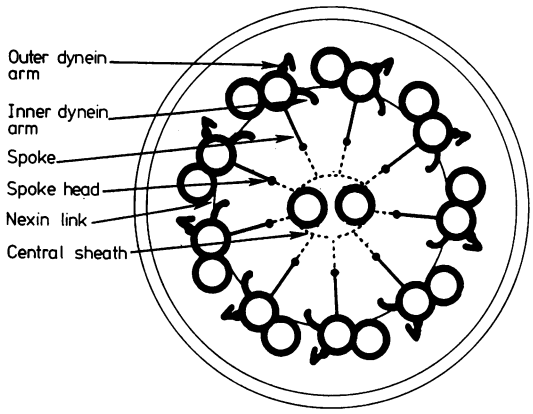

Figure *Diagrammatic cross-section through a cilium, showing the ultrastructure of the axoneme. Nine microtubular doublets are arranged in a circle around two central microtubules.*

The 9+2 microtubular elements run a straight course along the cilium (the axoneme does not twist). The direction of the ciliary beat is fixed relative to the 9+2 elements (the effective stroke of the ciliary beat is in the direction of doublets termed numbers 5 and 6). The microtubules are able to slide along each other as has been directly observed by Gibbons.[24] If sliding is induced but at the same time restrained by other bonds (such as the nexin links), then bending of the cilium will occur. The dynein arms have been shown to be the structures responsible for sliding of the doublets, whereas the interaction between spokes and the central sheath is believed to be responsible—together with the nexin links—for the conversion of the sliding into bending.

Immotile-cilia syndrome

During investigation of the semen from men with unexplained infertility, a few cases were found with sperm immotility and in which the sperm tail was devoid of dynein arms.[25 26] The central part of the sperm tail is an axoneme of the same type as that of the cilium. The absence of dynein arms explained why the spermatozoa were incapable of any movements and yet were living cells. It also led us to discover that cilia from the respiratory tract and elsewhere in these men showed the same defect. The affected individuals were also found to have suffered from chronic bronchitis and sinusitis from early childhood. Interestingly enough about half of the cases with these sperm and ciliary characteristics were found to have situs inversus; moreover some of them had bronchiectasis and could then be diagnosed as having Kartagener's syndrome (situs inversus, chronic sinusitis, bronchiectasis). Kartagener's syndrome can thus be regarded as a subgroup within a syndrome characterised by ciliary immotility. A name for the latter disease has been suggested: the immotile-cilia syndrome.[22] The prevalence of this syndrome has been estimated to be about 1:20 000, about twice as common as that of Kartagener's syndrome.[19]

Several tests have been performed to ensure that the term "immotile-cilia syndrome" is appropriate. Tracheobronchial mucociliary clearance has been measured and found to be practically or completely absent.[18] Light microscopical observations have been made of biopsies from the nasal and bronchial mucosa and no ciliary activity was seen. Electron microscopy has been performed of biopsies and two characteristics have been noted. One is the lack of the normal parallel orientation of the cilia. This means that the cilia would counteract, if they were able to beat and if it is true that the beat direction is determined by the orientation of the cilia. The other, and probably primary, characteristic is the defect of the ciliary machinery. In slightly more than half the investigated cases the two rows of dynein arms are missing. In other cases only one of the two rows of dynein arms (inner or outer) is missing, or else the spokes or the spoke heads plus the central sheath are absent.[27–29] The immotile-cilia syndrome is thus a heterogeneous disease. Different genes are involved and different proteins are missing in the biochemical motor. It is of interest that there is a connection between situs inversus and ciliary immotility and that this connection exists regardless of which protein is missing. It has been suggested that cilia on the embryonic epithelia have a fixed beat direction in normal embryos and that the beating is instrumental in determining the visceral situs. Without normal embryonic cilia chance alone will determine whether the viscera will take up the normal or the reversed position during embryogenesis.[19]

Clinical features of the immotile-cilia syndrome

The following description of respiratory tract symptoms is based mainly on an investigation of our first 14 patients with immotile cilia.[23] Among these were 10 men and four women, with an age range from 25-40 years. Five men and all women

had situs inversus. None had signs of other congenital malformations.

Respiratory tract disease could usually be traced back to early childhood, and in some cases there had been trouble with neonatal asphyxia. They had chronic cough and expectoration and rhinitis often complicated by nasal polyposis. Bronchitis and rhinitis were present in all 14 patients, chronic or recurrent maxillary sinusitis was present in all but one, and the frontal sinuses had often failed to develop. In many cases there was chronic or recurrent otosalpingitis or otitis media, with moderate decrease in hearing ability in half the patients.

Bronchiectasis had usually been acquired in childhood or adolescence (demonstrated in nine out of 14 cases; six operated). Surgical removal in selected cases resulted in marked improvement, although the chronic bronchitis of course was not cured. Recurrent pneumonia was fairly common. Three of the 14 cases had been treated for pulmonary tuberculosis. In several cases the symptoms of respiratory tract infection have been most severe in late childhood or adolescence—in adult life there was often partial remission of symptoms.

Ten of the 14 patients had overt obstructive lung disease as judged by spirometry. In a few there was severe effort dyspnoea, and in a man aged 31 years and a woman aged 32 years there was probably diffuse emphysema as judged by a reduced vascular pattern on chest radiographs. Thus severely impaired mucociliary transport directly predisposes to the development of chronic obstructive lung disease. Therefore it seems probable that the severely impaired mucociliary transport often present in common chronic bronchitis, and in many more or less symptom-free smokers as well, is directly involved in the development of the obstructive lung disease that may occur.

Half of the 14 patients were smokers or ex-smokers, and there was a tendency for lung function to be more impaired in them. We have subsequently seen a man aged 21 years who is a heavy smoker and has severe airways obstruction; we fear he will develop respiratory insufficiency within a few years if he does not stop smoking.

Most people with the immotile-cilia syndrome that we have investigated have been found to live an active life. General physical and mental development does not seem to have been retarded by the chronic disease. Patients with Kartagener's syndrome reaching old age have been described. Prognosis in the immotile-cilia syndrome is, therefore, probably hopeful in most cases—with modern medical care and without smoking it may even be excellent. It is also to be noted that situs inversus in the immotile-cilia syndrome is usually not combined with other congenital malformations, such as congenital heart disease.

For clinical purposes the diagnosis of the immotile-cilia syndrome can be regarded as established in (a) cases with complete Kartagener's syndrome, (b) men without situs inversus but with a typical clinical history (chronic bronchitis and rhinitis since early childhood) and with living but immotile spermatozoa, (c) women or children without situs inversus but with typical clinical signs and having a sibling with complete Kartagener's syndrome, and (d) individuals without situs inversus but with the clinical signs, if a nasal or bronchial biopsy shows characteristic ultrastructural defects in the cilia.

The immotile-cilia syndrome has many features in common with cystic fibrosis. However, the latter disease is more disabling and the prognosis is much worse. Mucociliary clearance is often impaired in cystic fibrosis, but is in most cases not completely absent as in the immotile-cilia syndrome. From a comparison between the two diseases it can be concluded that decreased mucociliary transport rate cannot be of primary pathogenic significance for the respiratory tract disease in cystic fibrosis.[30] From a similar comparison we may also conclude that impairment of mucociliary clearance cannot be of primary pathogenic significance in asthma; individuals with the immotile-cilia syndrome tend to develop chronic airways obstruction but not asthma. On the other hand it is still possible that impaired clearance is of great significance in exacerbations in asthma and in certain cases of severe chronic asthma complicated by cough and expectoration.

We conclude from these observations that death does not necessarily occur from failure of ciliary activity. It seems that cough and perhaps other mechanisms of tracheobronchial clearance can act as a partial substitute for severely damaged mucociliary clearance. On the other hand, mucociliary transport is an important defence mechanism of the airways and disease will develop when it fails. By comparing mucociliary clearance data, lung function data, and the clinical features in the immotile-cilia syndrome with corresponding data in other diseases of the respiratory system, information on the possible role of mucociliary clearance failure as a pathogenic factor in these latter diseases may be obtained.

BJÖRN A AFZELIUS AND BJÖRN MOSSBERG
Wenner-Gren Institute, University of Stockholm and Department of Thoracic Medicine, Karolinska Sjukhuset, Stockholm, Sweden

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